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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/692,807	10/20/2000	Ghazwan Saleem Butrous	PC10370A	6255

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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/692,807	BUTROUS ET AL.	
	Examiner	Art Unit	
	Dwayne C. Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12DEC2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date [illegible]
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 44-112 are pending.

2. Claims 44-112 are rejected.

Response to Arguments

3. Applicants' arguments November 4, 2004 have been fully considered but they are not persuasive with respect to the prior art teaching Ellis et al. Applicants present the following arguments. First, applicants submit the instantly disclosed claims are not anticipated by Ellis et al. of WO 94/28902, because Ellis et al. do not disclose the use of sildenafil for the treatment of pulmonary hypertension. Second, applicants argue that their claims are unobvious over Ellis et al. because Ellis et al. is not directed to selectivity of pulmonary hypertension over systemic hypertension. Third, applicants submit that even assuming arguendo that Ellis et al. make the Applicants' claimed subject matter "obvious to try", "obvious to try" is not the proper standard for patentability. Fourth, applicants argue additional references, namely Hansanato et al., which were not used in a rejection, to discuss state of the art and which allegedly does not teach or provide motivation for the skilled artisan in order to treat pulmonary hypertension.

4. First, applicants submit the instantly disclosed claims are not anticipated by Ellis et al. of WO 94/28902, because Ellis et al. do not disclose the use of sildenafil for the treatment of pulmonary hypertension. Foremost, the rejection of record is not under 35

U.S.C. 102 but rather under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902. The rejection of record was stated from the explicit teachings of Ellis et al. of using the same PDE inhibitor compound that is claimed by applicant, "[a] *particularly preferred group of compounds* of formula (I)" (emphasis added) is obtained when R^1 is methyl; R^2 is n-propyl; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). The rejection made the argument that sildenafil is embraced by these "*particularly preferred group of compounds* of formula (I)" by the prior art reference of Ellis et al, the "*particularly preferred group of compounds* of formula (I)" possess the same properties, PDE5 inhibitor, as that of the claimed compound, even though the prior art did not explicitly teach of this particular isozyme of PDE. The Ellis et al. invention is directed to the use of a series of pyrazolo[4,3-d]pyrimidin-7-one compounds for therapeutic treatment. Ellis et al. specifically cite, "The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). . . . This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in EP-A-046375 and EP-A-0526004, namely in the treatment of . . . hypertension, pulmonary hypertension.", (see page 2, 2nd full paragraph). The compounds of Ellis et al. are embraced by the structures of formula (I), (see pages 2-4). In particular, Ellis et al. of "[a] *particularly preferred group of compounds* of formula (I)" (emphasis added) is obtained when R^1 is methyl; R^2 is n-propyl; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the

nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). These "particularly preferred" compounds clearly embrace the instantly claimed pyrazolo[4,3-d]pyrimidin-7-one compounds of sildenafil. Ellis et al. also teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). Accordingly, these teachings render the instant claims obvious to one having ordinary skill in the art.

5. Second, applicants argue that their claims are unobvious over Ellis et al. because Ellis et al. is not directed to selectivity of pulmonary hypertension over systemic hypertension. However, Ellis et al. specifically teach inhibitors of cGMP PDEs with the compounds of formula (I) are used to treat inter alia, patients with pulmonary hypertension, (see page 2, 2nd full paragraph). Moreover, the skilled artisan would have been motivated and found it obvious to treat an individual that has pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan that these inhibitors of cGMP PDE are used to treat both hypertension and pulmonary hypertension.

6. Third, applicants submit that even assuming arguendo that Ellis et al. make the Applicants' claimed subject matter "obvious to try", "obvious to try" is not the proper standard for patentability. Due to the explicit teaching of Ellis et al. the skilled artisan is provided with motivation to use PDE inhibitors to treat pulmonary hypertension, (see page 2, 2nd full paragraph). Clearly, this provides the skilled artisan with ample motivation to use an inhibitor of PDE to treat pulmonary hypertension as well as giving

the artisan with an expectation of success of treating the ailment of pulmonary hypertension with "particularly preferred" compounds of formula (I) that clearly embrace the instantly claimed pyrazolo[4,3-d]pyrimidin-7-one compounds of sildenafil. In addition, this argument of "obvious to try" is not found persuasive due to the fact that Ellis et al. does not just recite a laundry list of PDE inhibiting compounds but specifically points direction and guidance to "particularly preferred" compounds of formula (I) that clearly embrace the instantly claimed pyrazolo[4,3-d]pyrimidin-7-one compounds of sildenafil.

7. Fourth, applicants argue additional references, namely Hansanato et al., which were not used in a rejection, to discuss state of the art and which allegedly does not teach or provide motivation for the skilled artisan in order to treat pulmonary hypertension. Since this reference was not used in a rejection it will not be addressed. Regarding the prior art references of EP 463,756 and EP 526,004, it is noted that these references were discussed because Ellis et al. states and teaches that cGMP-PDE clearly teach of treating hypertension and pulmonary hypertension and that the prior art references of EP 463,756 and EP 526,004 also disclose of PDE inhibiting compounds. Accordingly, this teaches to the skilled artisan that is known in the before the claimed invention that PDE inhibiting compounds, including the instantly claimed pyrazolo[4,3-d]pyrimidin-7-one compounds, are known to treat pulmonary hypertension.

Information Disclosure Statement

8. The information disclosure statements filed on December 12, 2005 has been reviewed and considered, see enclosed copy of PTO FORM 1449.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. The rejection of claims 44-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902 possessing a publication date of December 22, 1994, especially for "[a] particularly preferred group of compounds of formula (I)", which is a known PDE inhibitor, is maintained and repeated for both the above-stated and reasons of record. Ellis et al. teach of compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). This selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The skilled artisan would have been motivated to treat patients with pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan that these inhibitors of cGMP PDE are used to treat both hypertension and pulmonary hypertension. Ellis et al. specifically teach of inhibitors of cGMP PDEs with the compounds of formula (I). In fact, Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when R^1 is methyl; R^2 is n-propyl; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). Ellis et al. also teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). Ellis et al. teach of various modes of administration for these compounds,

inter alia, oral and parenteral administration, (see page 10). Ellis et al. further teach of a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. Accordingly, the Ellis et al. reference renders the instantly claimed invention obvious.

13. Claims 44-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schudt of U.S. Patent No. 6,333,354. Schudt teaches of a method of treating pulmonary hypertension with the administration of a composition that comprises at least a PDE inhibitor, (see claim 1). Schudt teach of the PDE inhibitor of sildenafil, (see column 2, line 10). In addition, Schudt specifically teach of "[o]ne embodiment of the invention is the combined use of a PDE inhibitor selected from the group consisting of vesnarione, zaprinast and sildenafil", (see column 3, lines 55-57). The skilled artisan would have been motivated to treat patients with pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan that these inhibitors ofPDE are used to treat the same ailment that is claimed in the instant application, namely pulmonary hypertension. In addition, Schudt teach of the administration of sildenafil without the administration of inter alia prostacyclines, oxgen, and iloprost, (see

column 2 and claim 1). The determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug while minimizing adverse and/or unwanted side-effects.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Wednesdays, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, may be reached at (571) 272-0951. The official fax No. for correspondence is (571)-273-8300.

Also, please note that U.S. patents and U.S. patent application publications are no longer supplied with Office actions. Accordingly, the cited U.S. patents and patent application publications are available for download via the Office's PAIR, see http://pair-direct.uspto.gov. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 1-866-217-9197 (toll free).

DWAYNE JONES
PRIMARY EXAMINER
Tech. Ctr. 1614
February 24, 2006